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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,512	02/08/2002	Tod M. Woolf	IVG-001	3457

959 7590 03/29/2005

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,512	WOOLF, TOD M.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,12-18,24,25 and 43-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,12-18,24,25 and 43-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 6/13/02; 12/16/02; 12/03/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application has been transferred to a new Examiner. Please direct further correspondence to Richard Schnizer, AU 1635.

An amendment was received and entered on 12/3/04.

Claims 3-11, 19-23, and 26-42 were canceled, and claims 43-54 were added as requested.

Claims 1, 2, 12-18, 24, 25, and 43-54 are pending in the application.

Applicant's election with traverse of group I is acknowledged. Applicant traverses "to the extent that Group I should be reformed as a single group containing presently pending claims 1, 2, 12-18, 24-25, and 43-54". Applicant has amended the presently pending claims to be drawn to methods of releasing an oligonucleotide from an endosomal vesicle, or endosome, in a cell. In view of this amendment, the restriction requirement is moot.

Claims 1, 2, 12-18, 24, 25, and 43-54 are under consideration in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12 and 13 are indefinite because they recite "the cells" without proper antecedent basis. Substitution of --cell is-- for "cells are" is suggested.

Claims 24 and 25 are indefinite because they recite "the fluorescent oligonucleotides" without proper antecedent basis. Substitution of -- fluorescent oligonucleotide is-- for "fluorescent oligonucleotides are" is suggested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 12, 13, 17, 18, 43, and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Berg et al (WO 96/07432, published 3/14/96), as evidenced by Weizman et al (J. Photochem. Photobiol. 59:92-102, 2000) or Moan et al (J. Photochem. Photobiol. 42:100-103, 1998).

Berg taught a method for releasing molecules into the cytosol of cells by allowing the molecules to be taken up into endosomes, treating the cells with a fluorescent photosensitizer that is conjugated to the molecule to be released, and which localizes to endosomes, and exposing the cells to light of a wavelength that excites the fluorescent

photosensitizer, resulting in release of the molecule form endosomes. Delivery-facilitating molecules such as carriers may also be present in the complex. See abstract, and paragraph bridging pages 2 and 3. Molecules for release include oligonucleotides such as ribozymes. See claim 2 on page 13. Regarding claims 2 and 49, ribozymes are double stranded to the extent that ribozymes form intrastrand double helices. Pertinent to claims 12 and 13, Berg exemplified light exposure of 30 seconds. See e.g. Fig. 13. Fluorescent photosensitizers include aluminum phthalocyanines such as $AlPcS2_a$ and sulfonated tetraphenylporphines such as $TPPS_1$ $TPPS2_a$, and $TPPS_4$. See e.g. page 5, liners 8-20, and structure I on page 9. Weizman provides evidence that sulfonated tetraphenylporphines are fluorescent. See abstract Moan provides evidence that $AlPcS2_a$ is fluorescent. See abstract.

Thus Berg anticipates the claims.

Claims 1, 2, 12, 13, 17, 18, 24, 25, 43, 45, 48, 49, 52, and 53 are rejected under 35 U.S.C. 102(e) as being anticipated by Berg et al (US Patent 6,680,301, issued 1/20/04), as evidenced by Weizman et al (J. Photochem. Photobiol. 59:92-102, 2000) or Moan et al (J. Photochem. Photobiol. 42:100-103, 1998).

Berg taught a method for releasing molecules into the cytosol of cells by allowing the molecules to be taken up into endosomes, treating the cells with a fluorescent photosensitizer that is conjugated to the molecule to be released, and which localizes to endosomes, and exposing the cells to light of a wavelength that excites the fluorescent photosensitizer, resulting in release of the molecule form endosomes. See abstract.

Molecules for delivery include oligonucleotides such as ribozymes. See column 2, lines 18-22, and claim 3 at column 23. Regarding claims 2 and 49, ribozymes are double stranded to the extent that ribozymes form intrastrand double helices. Delivery-facilitating molecules comprising basic amino acids, such as polylysine, may also be present in the complex. See column 7, lines 31-38. Berg exemplifies non-covalent complexes between polylysine and oligonucleotides. See Column 12, line 55 to column 13, line 7. The photosensitizer is conjugated to the molecule to be delivered, or to a carrier in separate embodiments. See column 2, lines 50-54. Pertinent to claims 12 and 13, Berg exemplified light exposure of less than 1 minute. See Fig. 17 and Fig. 24. Fluorescent photosensitizers include aluminum phthalocyanines such as $AlPcS2_a$ and sulfonated tetraphenylporphines such as $TPPS_1$ $TPPS2_a$, and $TPPS_4$. See e.g. column 6, lines 3-19, and structure (I) at column 9, lines 25-55. Pertinent to claims 24 and 25, Berg exemplifies an oligonucleotide concentration of 5.5 mM. See column 12, lines 25-31. Weizman provides evidence that sulfonated tetraphenylporphines are fluorescent. See abstract Moan provides evidence that $AlPcS2_a$ is fluorescent. See abstract.

Thus Berg anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 15, 18, 43, 47, 49, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) in view of Priest (US Patent 5,391,723, issued 2/21/95)

Berg taught a method for releasing molecules into the cytosol of cells by allowing the molecules to be taken up into endosomes, treating the cells with a fluorescent photosensitizer that is conjugated to the molecule to be released, and which localizes to endosomes, and exposing the cells to light of a wavelength that excites the fluorescent photosensitizer, resulting in release of the molecule form endosomes. See abstract. Molecules for delivery include oligonucleotides. See column 2, lines 18-22, and claim 3 at column 23. Delivery-facilitating molecules comprising basic amino acids, such as polylysine, may also be present in the complex. See column 7, lines 31-38. The photosensitizer is conjugated to the molecule to be delivered, or to a carrier. See column 2, lines 50-54.

Berg did not teach double stranded oligonucleotides consisting of two separate molecules, an oligonucleotide covalently modified with either a moiety that facilitates delivery to a cell, or with a fluorescently labeled polypeptide.

Priest taught the use of pH-sensitive covalent linkers to attach double stranded oligonucleotides to targeting proteins for delivery to cells. See abstract, and claim 1 at column 18.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the linkers of Priest in the method of Berg because the linkers are designed to degrade in lower pH environments such as endosomes, thereby releasing

the nucleic acids from the carriers. See column 7, lines 24-36. One would have been motivated to attach a fluorescent photoactivator to the targeting protein, because Berg suggests that carrier molecules can be modified that way. See e.g. column 2, lines 61-64.

Thus the invention as a whole was prima facie obvious.

Claims 1 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) in view of Parker et al (US Patent 4,541,438, issued 9/17/85).

Berg taught a method for releasing molecules into the cytosol of cells by allowing the molecules to be taken up into endosomes, treating the cells with a fluorescent photosensitizer that is conjugated to the molecule to be released, and which localizes to endosomes, and exposing the cells to light of a wavelength that excites the fluorescent photosensitizer, resulting in release of the molecule form endosomes. See abstract. Molecules for delivery include oligonucleotides. See column 2, lines 18-22, and claim 3 at column 23. Fluorescent photosensitizers include aluminum phthalocyanines such as $AlPcS2_a$ and sulfonated tetraphenylporphines such as $TPPS_1$ $TPPS2_a$, and $TPPS_4$. See e.g. column 6, lines 3-19, and structure (I) at column 9, lines 25-55.

Berg did not teach a flexible endoscopic light source.

Parker taught an endoscopic light source capable of delivering excitatory wavelengths of light for tetraphenylporphine sulfonates. See Figs. 4 and 5; and column 5, lines 33-44; and claims 22 and 30.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the endoscopic light source of Parker in the invention of Berg because Berg taught that any light source capable of emitting the appropriate wavelength light could be used. See column 7, lines 9 and 10. As such, Berg considered all such light sources to be equivalent. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was prima facie obvious.

Claims 1 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) in view of Flower et al (US Patent 6,443,976, issued 9/2/02).

Berg taught a method for releasing molecules into the cytosol of cells by allowing the molecules to be taken up into endosomes, treating the cells with a fluorescent photosensitizer that is conjugated to the molecule to be released, and which localizes to endosomes, and exposing the cells to light of a wavelength that excites the fluorescent

photosensitizer, resulting in release of the molecule form endosomes. See abstract. Molecules for delivery include oligonucleotides. See column 2, lines 18-22, and claim 3 at column 23. Delivery-facilitating molecules comprising basic amino acids, such as polylysine, may also be present in the complex. See column 7, lines 31-38. Fluorescent photosensitizers include aluminum phthalocyanines such as $AlPcS2_a$ and sulfonated tetraphenylporphines such as $TPPS_1$ $TPPS2_a$, and $TPPS_4$. See e.g. column 6, lines 3-19, and structure (I) at column 9, lines 25-55.

Berg did not teach the use of fluorescein.

Flower taught that radiation absorbing dyes such as fluorescein, phthalocyanines, and porphyrins were used to treat tumors in photodynamic therapies. Flower taught that these dyes functioned when contacted by excitatory light that caused the formation of singlet oxygen that subsequently damaged membrane components in close proximity to the dye. See detailed description paragraph 4. This principle is also disclosed by Berg at column 1, lines 34-53, and column 6, lines 1-43.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use fluorescein as a photosensitizer in the invention of Berg because Flower teaches that fluorescein functions similarly to the fluorescent activators of Berg, i.e. by producing singlet oxygen that damages membrane components in close proximity to the fluor. As such, fluorescein is a functional equivalent of the flours of Berg. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one

equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Because Berg teaches that the photosensitizer may be conjugated to the oligonucleotide delivery complex, it follows that the photosensitizer will localize to the endosomes with the oligonucleotide complex. So, one would have a reasonable expectation that the fluorescein would function to degrade the endosomes when contacted with excitatory light.

Thus the invention as a whole was prima facie obvious.

Claims 1, 18, 44, and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berg et al (US Patent 6,680,301, issued 1/20/04), in view of Furusako et al (US Patent 6,251,873, issued 6/26/01).

Berg taught a method for releasing molecules into the cytosol of cells by allowing the molecules to be taken up into endosomes, treating the cells with a fluorescent photosensitizer that is conjugated to the molecule to be released, and which localizes to endosomes, and exposing the cells to light of a wavelength that excites the fluorescent photosensitizer, resulting in release of the molecule form endosomes. See abstract. Molecules for delivery include oligonucleotides. See column 2, lines 18-22, and claim 3 at column 23.

Berg did not teach an oligonucleotide of 20-30 nucleotides in length.

Furusako taught 8 types of antisense oligonucleotides directed against CD14 ranging in length from 15-30 bases. See detailed description paragraph 103.

It would have been obvious to one of ordinary skill in the art to deliver the oligonucleotides of Furusako by the method of Berg because the method of Berg allows escape of oligonucleotides from the endosomal pathway, thereby avoiding degradation in lysosomes. With regard to the oligonucleotide lengths, Furusako taught oligonucleotides overlapping the claimed range. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).

Thus the invention as a whole was prima facie obvious.

Claims 1, 18, 43, 46, and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berg et al (US Patent 6,680,301, issued 1/20/04), in view of Burkly et al (US Patent 6,616,826, issued 9/9/03.

Berg taught a method for releasing molecules into the cytosol of cells by allowing the molecules to be taken up into endosomes, treating the cells with a fluorescent photosensitizer that is conjugated to the molecule to be released, and which localizes to endosomes, and exposing the cells to light of a wavelength that excites the fluorescent photosensitizer, resulting in release of the molecule form endosomes. See abstract. Molecules for delivery include oligonucleotides. See column 2, lines 18-22, and claim 3 at column 23. Delivery-facilitating molecules such as polylysine may also be present in the complex. See column 7, lines 31-38.

Berg did not teach complexes comprising HIV-TAT.

Burkly taught that polylysine and TAT peptides each function as gene delivery systems when complexed with nucleic acids. See detailed description paragraph 239.

It would have been obvious to one of ordinary skill in the art at he time of the invention to substitute the Tat peptide of Burkly for the polylysine of Berg because Burkly taught that both of these peptides functioned as gene delivery peptides. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was prima facie obvious.

Claims 1, 18, 43, 46, and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berg et al (US Patent 6,680,301, issued 1/20/04), in view of Burkly et al (US Patent 6,616,826, issued 9/9/03), and Rosenecker et al (US Published Application 20030125242, published 7/3/2003).

Berg taught a method for releasing molecules into the cytosol of cells by allowing the molecules to be taken up into endosomes, treating the cells with a fluorescent photosensitizer that is conjugated to the molecule to be released, and which localizes to

endosomes, and exposing the cells to light of a wavelength that excites the fluorescent photosensitizer, resulting in release of the molecule form endosomes. See abstract. Molecules for delivery include oligonucleotides. See column 2, lines 18-22, and claim 3 at column 23. Delivery-facilitating molecules may also be present in the complex. See column 7, lines 31-38.

Berg did not teach complexes comprising HIV-TAT, Antennapedia, or Transportan peptides.

Burkly taught that polylysine and TAT peptides each function as gene delivery systems when complexed with nucleic acids. See detailed description paragraph 239.

Rosenecker taught that HIV-TAT, Antennapedia, and Transportan were functionally equivalent for the purpose of transferring molecules into cells. See Summary of Invention paragraph 11.

It would have been obvious to one of ordinary skill in the art at he time of the invention to substitute the TAT peptide of Burkly for the polylysine of Berg because Burkly taught that both of these peptides functioned as gene delivery peptides. Similarly it would have been obvious to substitute either Antennapedia or transportan peptides in this manner in view of the teachings of Rosenecker indicating that TAT, Antennapedia, and Transportan were functionally interchangeable for this purpose. Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.